

# The Effect of General and Regional Anesthesia on the Neutrophil / Lymphocyte and Platelet / Lymphocyte Ratios During Bladder Tumor Surgery; Retrospective Study.

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## Research Article

**Keywords:** Bladder cancer, General anesthesia, Regional anesthesia, Systemic inflammatory response, Neutrophil/lymphocyte ratio, Platelet/lymphocyte ratio.

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# Abstract

**BACKGROUND:** Among the indicators of SIR are changes in the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR). This study aimed to determine the effect of general and regional anesthesia on SIR during short-term transurethral bladder resection (TUR-B) surgery.

**METHODS:** The 66 included patients were divided into 2 groups: Group 1 (general anesthesia) and Group 2 (regional anesthesia). The lymphocyte, platelet, and neutrophil counts before surgery and 1 h after surgery were obtained from the patients' records. The indicators of SIR the NLR and PLR were calculated preoperatively and postoperatively. Differences between the groups in the NLR and PLR were investigated.

**RESULTS:** At 1 h postsurgery there weren't any significant differences in the neutrophil, lymphocyte, platelet counts, or the NLR and PLR in groups, as compared to presurgery; however, the lymphocyte count was higher (but not significantly) in both groups, as compared to presurgery. The neutrophil count and NLR were lower (but not significantly) in Group 1 at postsurgery.

**CONCLUSIONS:** General and regional anesthesia have no effect on postoperative SIR in patients with bladder tumors that may require multiple surgeries and administration of anesthesia; however, we think larger scale prospective studies are needed to more clearly understand neutrophil count and NLR changes in bladder cancer surgery patients administered general anesthesia.

## Background

Despite ongoing advancements in cancer treatment, cancer remains an important health problem worldwide. Changes in cytokine and chemokine levels in cancer patients can lead to an increase in the neutrophil and platelet counts, and a decrease in the lymphocyte count [1]. These changes are indicative of systemic inflammatory response (SIR). The relationship between SIR, and tumor histopathology, invasiveness, and prognosis has been investigated in many cancer types. Hypoxia, necrosis, changes in neuro-endocrine metabolism, interleukin synthesis, and acute-phase protein production are the tumor-related factors thought to cause SIR [2]. Leukocytosis and systemic leucocytic changes, including neutrophilia and lymphopenia, can occur in response to surgery due to the action of various hormones and acute phase reactants. It is known that the degree of surgical trauma is associated with the production of immune mediators. Numerous studies report that general anesthesia suppresses the immune system [3]. Research on the effect of anesthesia methods and anesthetic drugs on tumor recurrence and metastasis is ongoing. It was reported that volatile anesthetics, such as sevoflurane and isoflurane, can block antigen-1-dependent integrin lymphocyte function and cause immune system suppression [4]. Moreover, such non-volatile anesthetics as ketamine suppress NK cell cytotoxicity and inhibit production of pro-inflammatory cytokines (IL-6 and TNF-a) [5].

Worldwide, bladder cancer is the 9th most common cancer [6]. Among bladder cancers, 75%-85% are non-muscle invasive bladder cancers. The effects of some prognostic factors, such as positive cytology,

immunological and molecular features, and tumor grade, on SIR in bladder cancer patients have been investigated [7,8]. Bladder cancer patients may need to undergo multiple surgeries and administration of anesthesia. Recently, changes in the neutrophil, lymphocyte, and platelet counts, and neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte (PLR) have been used as inexpensive and reliable prognostic indices of SIR in patients undergoing transurethral bladder resection (TUR-B) surgery [9].

Although the effect of inhalation anesthetics and intravenous anesthetics on SIR has been studied, to the best of our knowledge no study has investigated the effect of regional anesthesia and general anesthesia on the NLR and PLR. The aim of the present study was to determine if general anesthesia and regional anesthesia differentially affect SIR in patients undergoing TUR-B surgery. The study included patients undergoing short-term TUR-B surgery so as to minimize the effect of surgical trauma, because bladder tumor patients can require multiple surgeries and administration of anesthesia.

## Patients And Methods

Patients that underwent TUR-B surgery due to bladder cancer between 1 June 2018 and 1 June 2019 were retrospectively reviewed. Data were obtained from hospital and clinical records. In total, there were 108 bladder cancer patients that underwent TUR-B, of which 21 had muscle invasion. In addition, pathology was benign in 9 cases. As such, 78 patients with non-muscle invasive bladder cancer (NMIBC) were selected. Patients aged >18 years, and those with chronic use of steroids, use of analgesics, a history of chemotherapy or radiotherapy, a coagulation disorder, hypo- or hyperthyroidism, diabetes mellitus, and infection were excluded from the study. The remaining 66 patients were divided into 2 groups: Group 1 (general anesthesia [n = 31]) and Group 2 (regional anesthesia [n = 35]).

Midazolam 1-2 mg (Dormicum® 5 mg 5 mL<sup>-1</sup>, Roche, Switzerland) was administered to all patients for premedication. Group 1 was administered fentanyl 0.2-0.3 µg kg<sup>-1</sup> (talinat 0,5 mg mL<sup>-1</sup> 10 mL, Vem, Istanbul), propofol 2-3 mg kg<sup>-1</sup> (propofol 1%, Fresenius, Sweden), sevoflurane 1-2 MAC (Sevorane 100%, AbbVie, England), and remifentanyl 2-4 ng kg<sup>-1</sup> (rentanil 2 mg, Vem, Istanbul). For maintenance 40%/60% oxygen/air mixture was administered and a laryngeal mask was used during induction. Group 2 was administered hyperbaric bupivacaine 12,5 mg (Marcaine® Spinal Heavy 0.5%, AstraZeneca) via a 25-gauge Quincke needle from the lumbar 4-5 or lumbar 3-4 range.

Age, gender, ASA (American Society of Anesthesiologists) value, surgical duration, the presurgery and 1 h postsurgery lymphocyte, platelet, and neutrophil counts, and the hematocrit value were obtained from the patients' records. The markers of SIR—NLR and PLR—were calculated presurgery and 1 h postsurgery, and then compared. The study protocol was approved by the local ethics committee (2019-08/389) and all patients provided verbal consent.

## Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows v.21 (IBM Corp., Armonk, NY). Numerical data are shown as mean  $\pm$  SD or median (range), whereas categorical data are shown as number and percentage. The Kolmogorov Smirnov test was used to determine the normality of the distribution of data. When parametric assumptions were met, pre- and postsurgery comparison of 2 independent numerical variables was performed via two-way analysis of variance in repeated measures. To compare 2 independent groups the significance test (student's t-test) of the difference between the 2 means was applied. When parametric assumptions were not met the Wilcoxon test was used for pre- and postsurgery comparison of numerical variables and the Mann-Whitney U test was used for comparison of 2 independent groups. The chi-square test was used to compare categorical variables. The level of statistical significance was set at  $P < 0.05$ .

## Results

Age, gender, and surgical duration did not differ significantly between groups 1 and 2 ( $P = 0.172$ ,  $P = 0.770$ ,  $P = 0.230$ , respectively), nor did ASA distribution (ASA I, II, and III, respectively in group 1/2:  $n = 2/3$ , and  $18/20$ , and  $11/12$ ). In both groups there wasn't a significant difference between the presurgery and postsurgery neutrophil, lymphocyte, and platelet counts or the hematocrit value ( $P = 0.084$ ,  $P = 0.676$ ,  $P = 0.459$ , and  $P = 0.495$ , respectively). There weren't any significant differences in presurgery-postsurgery change in the hematocrit value, the lymphocyte, neutrophil, and platelet counts, or NLR and PLR between groups 1 and 2 ( $P = 0.084$ ,  $P = 0.676$ ,  $P = 0.459$ ,  $P = 0.471$ , and  $P = 0.562$ , respectively) (Table and Figures 1-5).

Presurgery-postsurgery change in the hematocrit value was considered a reference for intraoperative bleeding and fluid treatment. The lymphocyte count increased slightly in both groups postsurgery. The postsurgery neutrophil count was lower than the presurgery count in Group 1, but the difference was not significant. The NLR did not change postsurgery in Group 2, but decreased in Group 1; however, the difference was not significant (presurgery/postsurgery NLR in Group 1 was  $2.76/2.47$ , versus  $2.44/2.45$  in group 2 [ $P = 0.471$ ]) (Table and Figure 4). The PLR decreased postsurgery in both groups similarly, as compared to presurgery (presurgery/postsurgery PLR in Group 1 was  $136.61/127.81$ , versus  $149.44/131.86$  in Group 2 [ $P = 0.562$ ]) (Table and figure 5).

## Discussion

The present findings show that there wasn't a significant difference in the neutrophil, lymphocyte, and platelet counts, or the NLR and PLR between the presurgery and 1 h postsurgery in both anesthesia groups.

Yamanaka et al. [10] reported that patients who have gastric cancer with a NLR  $<2.56$  were SIR negative and those with a NLR  $\geq 2.56$  were SIR positive. They also reported that the NLR ratio is an independent prognostic factor in patients with advanced-stage gastric cancer. Measurement of the NLR might serve as

a clinically accessible and useful biomarker of patient survival. In the present study 1 h postsurgery the NLR was  $<2.56$  in both anesthesia groups, indicating that SIR was not present.

Smith et al. [11] reported that patients who have periampullary malignancy with a PLR  $<150$  were SIR negative and those with a PLR  $\geq 150$  were SIR positive. They further reported that the preoperative PLR are indicators of tumor invasiveness and the requirement for laparoscopic staging in patients with potentially resectable periampullary malignancy. When they combined the requirement for both the CA19-9 level  $\leq 150$  kU/l and PLR to be  $\leq 150$  (38 out of 183), both the positive predictive value (95%) and specificity (96%) improved (Fisher's exact test  $P = 0.065$  and  $P < 0.001$ , respectively); 21% of laparoscopies were avoidable when using these criteria. In the present study the PLR was  $<150$  in both groups in preoperatively and postoperatively.

Some researchers have investigated the effect of regional anesthesia on SIR and postoperative complications. Bedirli et al. [12] investigated the effect of thoracic epidural anesthesia (TEA) on SIR and consequent postoperative lung complications in rats, reporting that TEA reduces SIR by reducing plasma TNF- $\alpha$ , IL-6, and IL-1 $\beta$  concentrations, which prevents postoperative pulmonary complications. These effects are due to a decrease in apoptosis, ICAM-1 release and proinflammatory cytokine release, and an increase in antioxidant enzyme activity. The researchers posited that these effects are not due to sympathetic block, but may be due to the systemic effect of bupivacaine. In the present study there weren't any postsurgery changes in SIR parameters in the Group 1 patients given bupivacaine.

Researchers have sought to determine if the effects of general and regional anesthesia on SIR differ. One such study included 40 patients that underwent total knee arthroplasty [13]. SIR parameters IL-6, IL-8, and IL-1 $\beta$ , TNF- $\alpha$ , and C-reactive protein (CRP) were measured before induction, immediately after surgery, and 24 h postsurgery. In both the general and regional anesthesia groups IL-6 and CRP increased significantly at 24 h postsurgery, as compared to presurgery. As noted in the present study, the effect of general and regional anesthesia on SIR did not differ; however, the present study used the NLR and PLR as SIR parameters.

Measurement of the NLR and PLR are both readily available and inexpensive methods for investigating SIR. Solakhan et al. [14] investigated the relationship between SIR, and tumor histology and pathogenesis in patients that underwent TUR-B surgery for bladder tumors. They observed that the NLR and PLR can be used as SIR parameters. The platelet count can increase in patients with solid tumors as a result of the inflammatory response. The IL-6 thrombopoietic cytokine can be released by tumor cells. Platelets can facilitate metastasis by protecting tumors from NK cell lysis and, in association with the biological factors involved, can also contribute to tumor growth, invasion, and angiogenesis. The prognosis and surveillance of many cancers such as colorectal, ovarian, lung, and hepatocellular cancer are related to PLR (13,14); yet, the mechanism is not specific. Platelets can enhance tumor growth by stimulating angiogenesis via vascular endothelial factor (VEGF) [15]. An increase in the preoperative NLR is associated with advanced stage in non-small cell lung cancer patients, but is an independent indicator of

survival following complete resection [16]. The NLR is a potential biological marker of high risk of mortality in stage I patients.

The NLR and PLR are used as prognostic markers in many types of cancer surgery, as well as for preoperative surgical staging. Ertas et al. [2] noted a higher NLR and PLR in gynecological cancer patients with lymph node involvement than the patients without lymph node involvement. Expert that the NLR is superior to the PLR in terms of sensitivity and specificity. Again, they proved the connection between tumor size and the NLR. The present study included patients with bladder cancer of similar pathogenesis based on the assumption that patients with bladder cancer of varying pathogenesis may have SIR parameters that differ.

Mano et al. [17] posited that the NLR could play a role in predicting recurrence in patients with bladder tumors. They found that the recurrence rate was higher in the patients with a high NLR ratio. The present study aimed to determine which anesthesia technique (general versus regional) affects the NLR the least.

In addition, the effects of anesthesia types on SIR and tumor prognosis like surgical types are investigated. The effects of TIVA (total intravenous anesthesia) and volatile anesthetics on postoperative SIR, postoperative complications, and duration of hospitalization were studied in patients that underwent surgery for pancreatic cancer. During the 90-d postoperative follow-up period fewer postoperative complications were observed in the patients that underwent TIVA, although preoperative and postoperative NLR and PLR values did not differ between the 2 groups [18].

Kim et al. [19] studied the effect of TIVA and sevoflurane volatile anesthesia on preoperative and postoperative NLR and PLR in 40 patients that underwent endoscopic vaginal hysterectomy. The total leukocyte count, neutrophil count, and NLR significantly increased, and the lymphocyte count significantly decreased in both groups immediately after surgery, 2 h postsurgery, and 24 h postsurgery. The neutrophil count and NLR were lower in the TIVA group. Their findings show that TIVA has less of an effect on SIR than sevoflurane anesthesia. In the present study there weren't any differences in the SIR parameters at 1 h postsurgery between the 2 anesthesia groups. A study on the effect of paravertebral block + propofol versus inhalation anesthesia + opioid use on the postoperative NLR was compared in patients that underwent surgery for breast cancer [20]. The preoperative NLR was similar in both groups, but the postoperative NLR was lower in the paravertebral block + propofol group (mean: 3.0 [range: 2.4-4.2] vs. mean: 4.0 [range: 2.9-5.4],  $P = 0.001$ ). Propofol-paravertebral anesthesia attenuated the postoperative increase in the NLR, but the effect was not significant. In the present study the NLR was lower in the general anesthesia group at 1 h postsurgery, whereas in the regional anesthesia group it did not change, but the difference was not significant. It was also observed that the PLR was lower postsurgery as compared to presurgery in both anesthesia groups.

## Conclusion

In conclusion, the present findings show that there isn't a relationship between general or regional anesthesia, and the NLR or PLR in bladder cancer patients that undergo TUR-B surgery. It was also noted

that general and regional anesthesia techniques do not affect postoperative SIR following TUR-B surgery for bladder tumors. The NLR and PLR are inexpensive and simple-to-use laboratory methods for evaluating SIR; however, we think that larger scale prospective studies are needed to more clearly delineate how general anesthesia and regional anesthesia differentially affect the NLR and PLR postsurgery.

## Declarations

**Ethics approval:** This study was approved by the ethics committee of T.C. Ministry of Health Provincial Health Directorate Dr. Abdurrahman Yurtaslan Ankara Oncology Health Application and Research Center with approval number [2019-08/389].

The patients provided verbal consent. Written consent of the patients was not required as it was a retrospective study. All methods were carried out in accordance with Declaration of Helsinki.

**Consent for publication:** Not applicable

**Availability of data and materials:** All data generated or analysed during this study are included in this published article [if someone wants to request the data, it should be contact with [guldargun@yahoo.com](mailto:guldargun@yahoo.com) address].

**Competing interests:** The authors declare that they have no financial and non-financial competing interests regarding the publication of this article.

**Authors' contributions:** The work was designed by GA. GA, MD analysed of data. FH prepared figures 1-5. EK provided the interpretation of data. GA wrote the main manuscript. SU and HB have drafted the work or substantively revised it. All authors read and approved the final manuscript.

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## Tables

**Table.** Demographic characteristics, and preoperative and postoperative variables according to group

Variables		Group 1 (general anesthesia) (n = 30) Median(range)or n (%)	Group 2 (regional anesthesia) (n=36) Median(range)or n (%)	P
ASA I, II, III		2, 18, 11	3, 20, 12	
Mean Age (years)		65.39 ± 9.32	64.47 ± 12.79	0.172
Gender (female/male)		6 (20.0)/24 (80.0)	9 (25.0)/27 (75.0)	0.770
Mean surgical duration (min)		72.25 ± 11.02	70.68 ± 10.09	0.230
Neutrophil count	Before	5.45 (3.10-15.85)	4.90 (0.49-14.04)	0.084
	After	4.88 (1.73-23.70)	4.79 (2.43-14.90)	
Lymphocyte count	Before	1.92 (0.26-3.50)	1.88 (0.51-5.55)	0.676
	After	2.07 (0.29-3.34)	2.01 (0.52-3.74)	
Platelet count	Before	269.50 (117-648)	247.50 (152-603)	0.459
	After	249 (37-548)	243 (127-546)	
NLR	Before	2.76 (1.48-22.35)	2.44 (0.09-14.33)	0.471
	After	2.47 (0.97-17.61)	2.45 (1.12-22.58)	
PLR	Before	136.61 (58.71-450)	149.44 (41.62-470.59)	0.562
	After	127.81 (49.40-396.67)	131.86 (56.42-689.39)	
Hematocrit	Before	41.90 (31.40-46.10)	40.85 (30.45-49.00)	0.495
	After	41.66 (30.20-48.20)	41.50 (31.40-48.20)	

## Figures

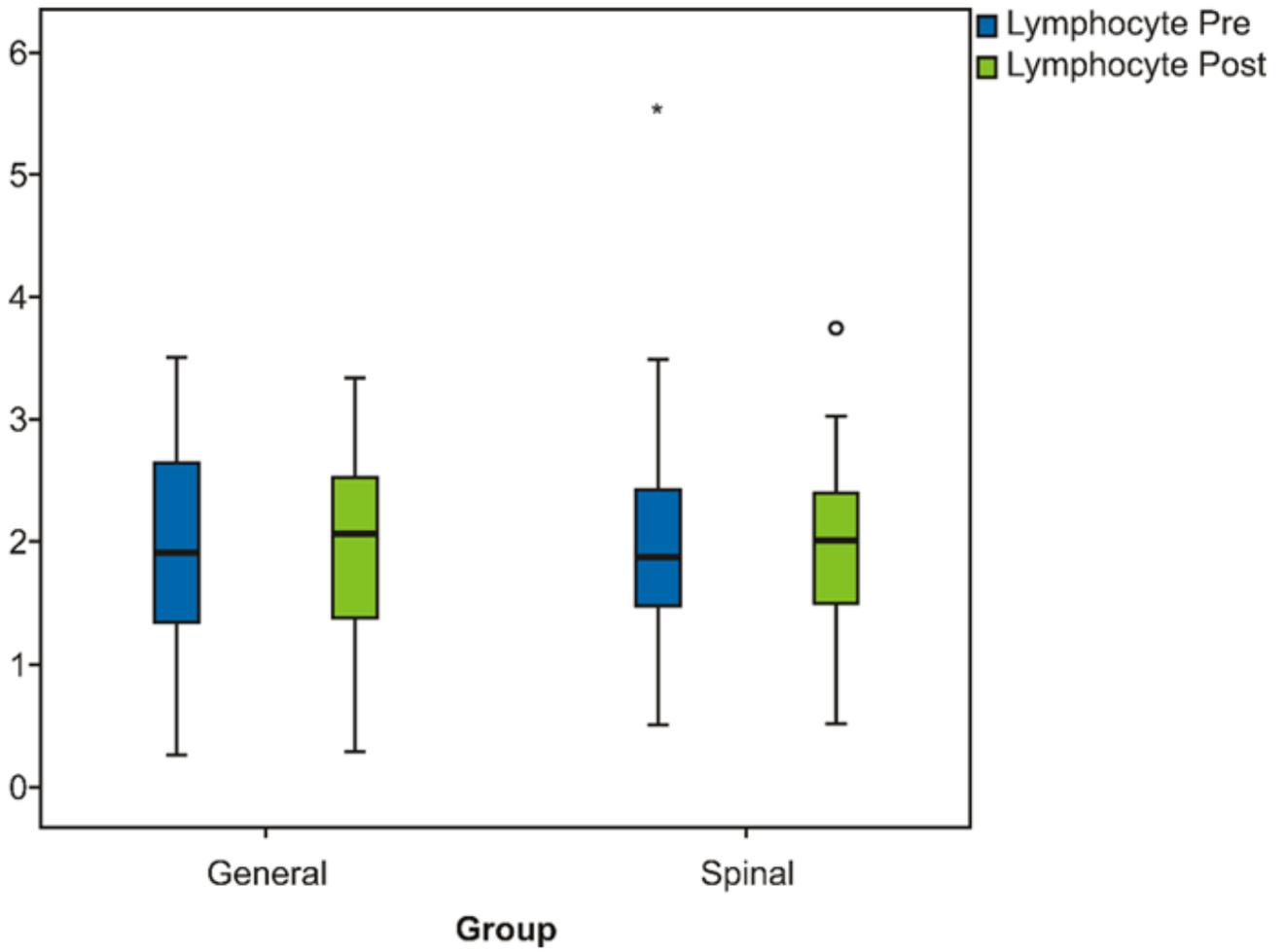
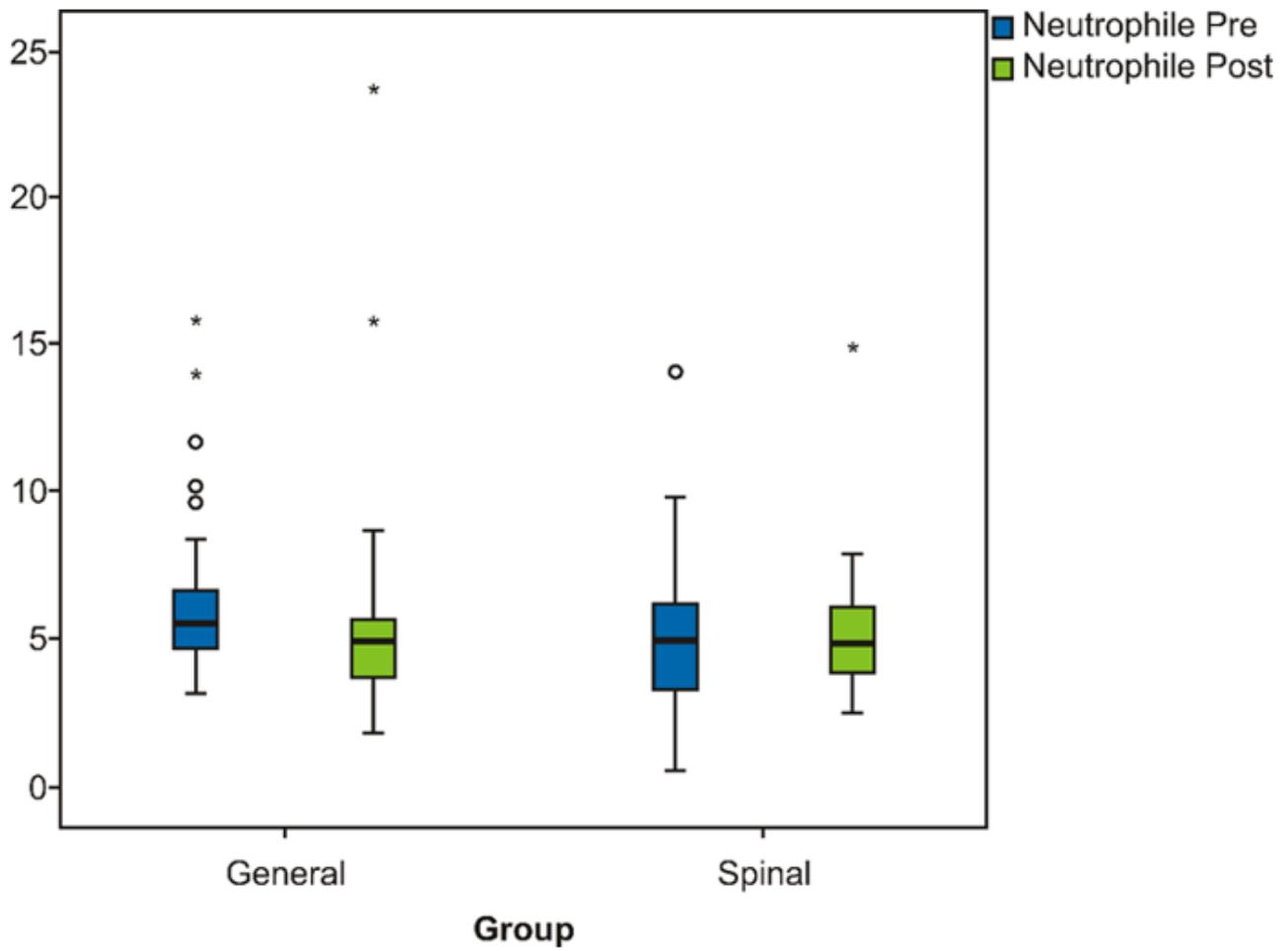


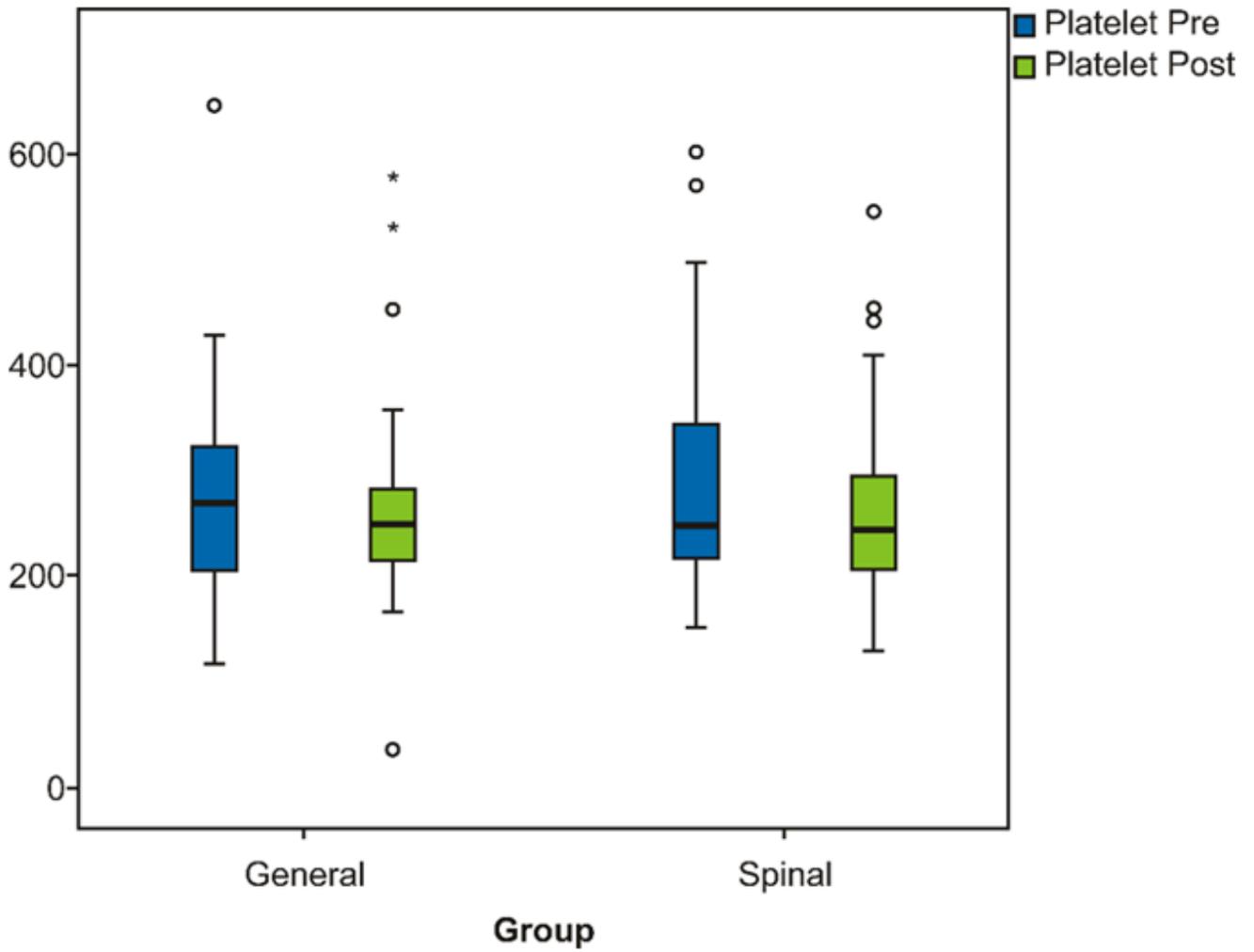
Figure 1

Preoperative and postoperative lymphocyte counts in the general and regional anesthesia groups



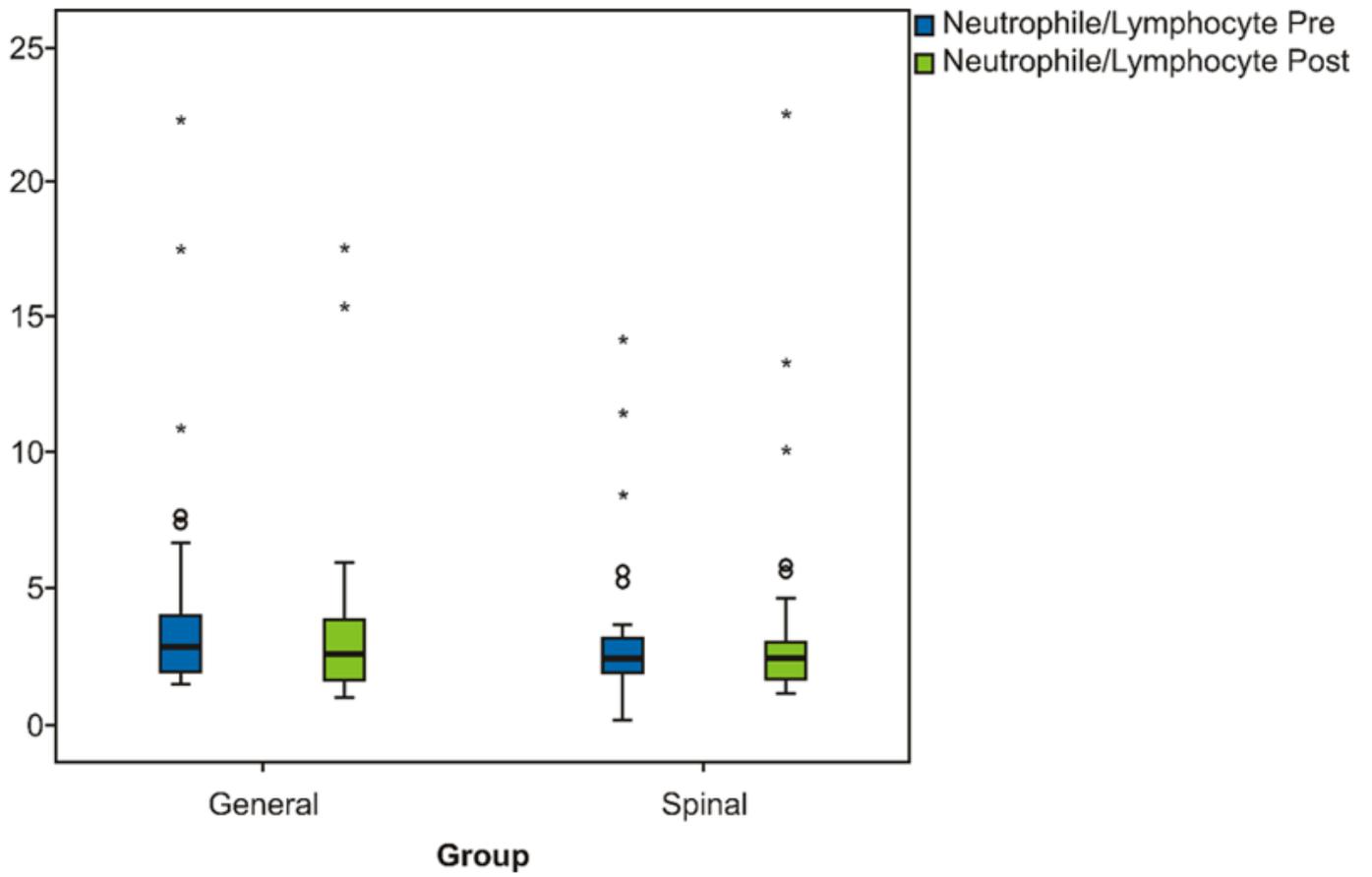
**Figure 2**

Preoperative and postoperative neutrophil counts in the general and regional anesthesia groups



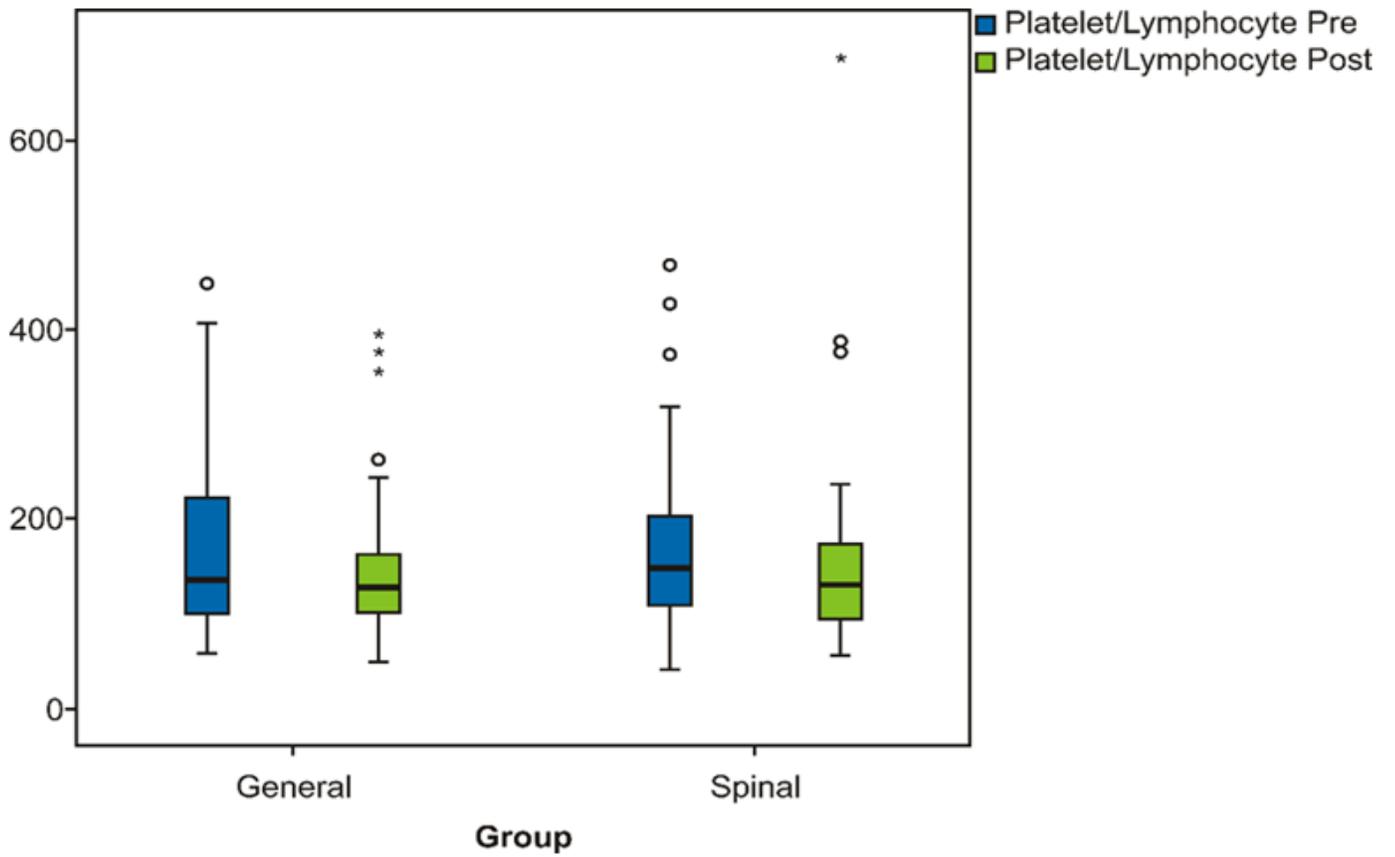
**Figure 3**

Preoperative and postoperative platelet counts in the general and regional anesthesia groups



**Figure 4**

Preoperative and postoperative NLRs in the general and regional anesthesia groups



**Figure 5**

Preoperative and postoperative PLRs in the values general and regional anesthesia groups